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Original article

CURRENT APPROACHES TO SCHIZOPHRENIA

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Abstract

Schizophrenia is a psychotic disorder (or a group of disorders) marked by the serious impairment of thought, emotions andbehavior. Most schizophrenics, if not treated, gradually withdraw from interactions with other people, and lose the ability to take care of personal needs and care.

The use of estrogen as a potential treatment for schizophrenia opens new opportunities for both preventive treatment and acute treatment of schizophrenia in men and women. There are still considerable studies to be made to determine the correct dose and duration of estradiol use for its safe use in women and men with schizophrenia in terms of known side effects and whether it can eventually be used as an independent drug, as an adjuvant.

The results of the studies provided strong evidence for the estrogen protection hypothesis, and the addition of transdermal estradiol was associated with a significant reduction in psychotic symptoms in patients with DSM-IV schizophrenia compared to standardized treatment with antipsychotic drugs.

The physiotherapist, as a member of an interdisciplinary team, through the exercise program that he provided, improved the physical mental health of patients. Physiotherapists are experts in physical health, which provide an important step between physical and mental health in patients with schizophrenia.

*Key Words:*Hormone Estrogen, schizophrenia, neuro-protection.

Introduction

Neuro-protection in this context is an important concept in the treatment of patients in the early, prodromal phase of psychosis. Neuro-protection as describedhererefersto theuse of agentsto control the process of apoptosis, whichoccurs more rapidly in theearliestphases of schizophrenia. Thereis a need to identify medications with fewer side effects than anti-psychotics in ordertotreat at risk mental states or prodromalpsychosis. Studies have shown that schizophreniaoccurs in males at an earlier age than females. Later, at abou the time of the menopause, thereis a second peak in the incidence of psychosis (schizophrenia) in women. Hence it has been suggested that estrogen hormone maybe neuroprotective. Studies have shown that the addition of oestradiolto anti-psychotics in thetreatment of schizophrenia in females increased the efficacy of the treatment which suggests that estrogen hormone does indeed have a neuroprotective action.

Purpose of the study

To establish whether there is evidence that estrogen hormone is neuroprotective and can be used in treating early (prodromal) schizophrenia, or as an adjunct in treating schizophrenia itself.

Research Methods

Literature search using Google Scholar. It is fully acknowledged that this article is a review in order to answer to the purpose of this congress paper and as such is entirely dependent on the work of the original authors, particularly Berger, Hafner, Kulkarni, and others, all of whom are fully referenced and acknowledged in the text.

Neuroprotection questions

The concept of Neuroprotection is new to psychiatry. So far it has been applied to Neurological conditions. Neuroprotection refers to modulation of the regulatory processes of growth, regeneration and survival of brain cells that might be at risk of damage or even death. Berger (2007) provided histological evidence that neurodegeneration in neurological disorders is mediated by cell necrosis, with subsequent gliosis (Berger 2007). This is not so in the early phase of psychotic illness, in which apoptosis is an important process which regulates brain development and synaptic plasticity. In conditions such as schizophrenia or bipolar affective disorders, there is no sign of gliotic changes at post mortem even after years of illness (Berger 2007). Neuro-protection is an important concept in the treatment of patients in the

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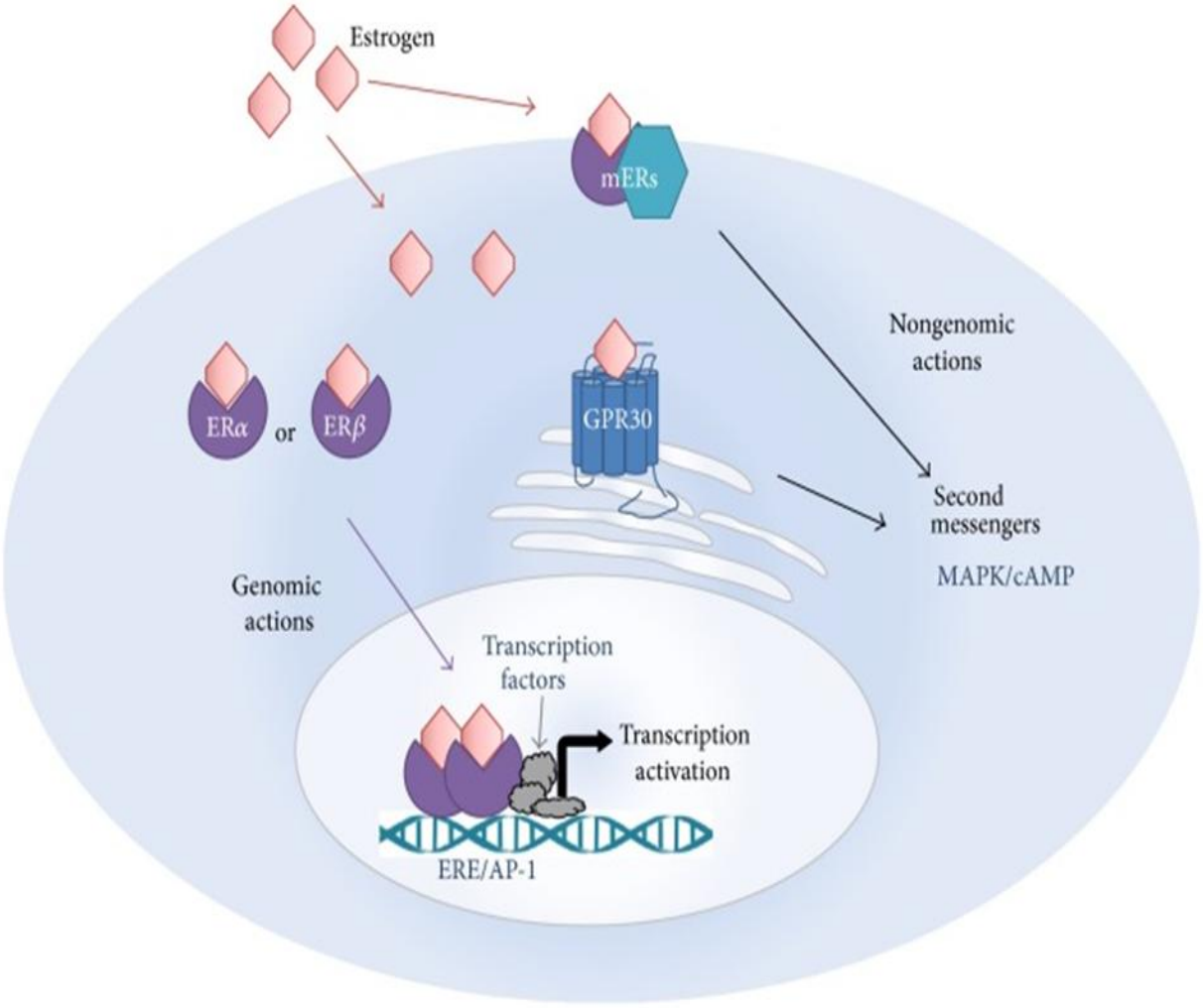
early, prodromal phase of psychosis, otherwise known as the 'At Ultra High-Risk Mental State'. Neuro-protection as described here refers to the use of agents to control the process of apoptosis, which occurs more rapidly in the earliest phases of schizophrenia. There is a need to identify medications with fewer side effects than anti-psychotics in order to treat at risk mental states, or prodromal psychosis if safe treatments for this stage of the illness state are to be produced (Berger 2007). Berger et al have conducted a systematic literature search in order to identify neuroprotective agents with a more favorable side effect profile than Atypical Antipsychotics. This list would then provide a basis for further research (Berger 2007).

Estrogen hormone is an example of a substance which has been proposed to have neuroprotective action because of the observed epidemiology of schizophrenia. A number of epidemiological studies have shown that schizophrenic psychoses begin on average 4–5 years later in women than in men (Hafner 1991).



Putative mechanisms of estrogen action in the cell. Estrogen can act via either genomic or nongenomic mechanisms. Genomic mechanisms involve activation of the estrogen receptors (ERs) by estrogen, which then translocate to the cell nucleus as hetero- or homodimers to bind to estrogen response elements (EREs) or to activator protein 1 (AP-1) sites, resulting in transcription activation. Nongenomic actions occur via binding of estrogen to ERs or to a G protein coupled receptor GPR30, either intracellularly or at the plasma membrane (mERs) to activate second messenger systems, such as those involving mitogen-activated protein kinase (MAPK) or cyclic adenosine 3′,5′-monophosphate (cAMP) pathways, which can also activate transcription or have other effects.

Research study

Dr J Kulkarni and colleagues from The Alfred Hospital, Monash University's School of Psychology, Psychiatry and Psychological Medicine and Monash Medical Centre, Melbourne, Australia, carried out the research. Funding was provided by the Stanley Medical Research Institute and the National Health and Medical Research Council of Australia. The study was published in the peer-reviewed medical journal: Archives of General Psychiatry.

The study

This was a double blind randomized controlled trial designed to look at the effects on psychotic symptoms in women with schizophrenia of applying either an estrogen hormone patch or placebo patch to the skin, alongside standard treatment.

The researchers recruited 102 women to the study from inpatient and outpatient units of two hospitals in Melbourne. All women had verified diagnoses of schizophrenia or a related schizophrenia type condition and all were diagnosed to have severe illness, including some who had not responded to previous treatments. The researchers excluded those women with a bipolar subtype of illness (although they included those with a depressive subtype), those currently receiving hormone treatment such as the pill, those pregnant or breastfeeding, those around the time of menopause, those with overactive thyroid and any with an unstable medical condition.

The women were randomly assigned to receiving either a 100 microgram per day estrogen hormone patch (56 women) or a placebo patch (46 women) for four weeks. Neither the women or the research team were aware of which treatment they were receiving. Other antipsychotic medications were continued. The researchers used a recognized assessment scale (Positive and Negative Syndrome Scale; PANSS) to look at psychotic symptoms at the start of the study and then once weekly for four weeks. On this scale, positive symptoms include such things as hallucinations, delusions, disorganized thinking, negative symptoms include things such as reduced emotional response, emotional and social withdrawal; and general symptoms are things like anxiety, depression, and poor control of impulses. Side effects of treatment were assessed at each follow up, and blood samples were taken to look at hormone levels at the beginning and end of the study. Statistical tests were used to look at differences in symptoms and side effects between the groups.

Study results

In all, after some dropouts and exclusions, 85.3% of the 102 women were analyzed at the end of the study (91% of the treatment group and 78% of the placebo). There were no differences between the women in either group in terms of age, severity or duration of illness, medication used, or menstrual cycle phase at the beginning of the study.

Outcome measure	Studies *N*	Subjects *N*	Hedges' *g* (95% CI)	*p*-value	I^2	Q-value (*p*-value)	Egger's test
PANSS[a]							
Positive	**9**	**561**	**0.32 (0.05–0.59)**	**0.02**	**54.24**	**17.48 (0.03)**	**0.11**
Negative	**9**	**561**	**0.40 (0.08–0.72)**	**0.02**	**67.23**	**24.42 (0.002)**	**0.03**
General	**7**	**526**	**0.46 (0.01–0.82)**	**0.01**	**74.01**	**23.08 (0.001)**	**0.005**
Total	**8**	**482**	**0.57 (0.41–0.99)**	**0.009**	**77.51**	**31.12 (<0.001)**	**0.05**
Depression	2	135	0.14 (−0.20–0.47)	0.43	N/A	0.33 (0.57)	N/A
Cognition							
Attention and working memory	4	352	−0.01 (−0.28–0.26)	0.92	27.25	4.12 (0.25)	0.66
Executive functioning	2	221	0.03 (−0.23–0.29)	0.83	N/A	0.42 (0.52)	N/A
Memory	4	361	0.12 (−0.11–0.35)	0.31	13.22	3.46 (0.33)	0.16
Psychomotor speed	3	303	0.28 (−0.26–0.81)	0.31	74.68	7.90 (0.02)	0.28
Verbal fluency	4	361	0.06 (−0.24–0.35)	0.71	41.58	5.14 (0.16)	0.83
Global cognitive functioning	2	256	−0.13 (−0.37–0.11)	0.30	N/A	0.22 (0.64)	N/A

N number, PANSS Positive and Negative Syndrome Scale. Significant effect sizes in bold. N/A not applicable
[a]Not all studies reported all PANSS scales, therefore, the number of studies varies between subdomains

Compared to the placebo group, women who received estrogen hormone had significantly greater improvement over time in overall symptoms, and also in positive symptoms (as measured with the PANSS total score, positive symptom score and general psychotic symptom score). There was no difference between the groups in negative symptoms as measured on the PANSS. There was no difference in rate of adverse side effects between the groups.

Thus, Kulkarni's work suggested that Estradiol appears to be a useful treatment for women with schizophrenia and may provide a new adjunctive therapeutic option for severe mental illness.

Discussion

All the above data suggest that there are a number of differences in the manifestations of schizophrenia between men and women, and that these differences may be explained by the neuroprotective effect of estrogen hormone during the reproductive years of a woman's life. These effects disappear in the peri and post-menopausal periods when the effects of estrogen hormone are no longer present. Estrogen hormone has been described as a mild antipsychotic and has been compared to the atypical anti-psychotics. It has been shown to exert a neuromodulator effect bydowngrading dopamineneurotransmission and causing an increase in serotonin receptors. Estrogen hormone has also been postulated to have a positive effect on short- and long-term verbal memory in postmenopausal women, as well as increasing the capacity for new learning. Since cognitive deficits are a major problem for women with schizophrenia, estrogen hormone replacement therapy may have an added benefit for postmenopausal women with schizophrenia (Sherwin 2001).

Kulkarni reports a study on the Global Assessment of Function in 350 patients with established schizophrenia. These scores were significantly better in women, although overall, they were only in the mild to moderate range of function (Kulkarni 2001). The difference in GAF scores between the genders may reflect a difference in the premorbid functioning of patients, which may be a product of the age difference at the onset of the illness. Kulkarni reported on the quality of life (Kulkarni 2001) in the same group of 350 patients with schizophrenia using the Quality of Life Scale (QLS). Women were found to have a higher quality of life, according to this scale, than men. Women with schizophrenia scored better than men in the areas of interpersonal relations, instrumental role, and activities. There were no significant gender differences in life satisfaction, social needs, and basic needs. After 12 months, data on the quality of life of the same patients showed no significant difference between men or women with schizophrenia. None of the QLS subsections on interpersonal relations, instrumental role, activities, and intrapersonal activities such as motivation, empathy, or curiosity had improved, despite the fact that the actual psychotic symptoms had improved. It must be assumed that estrogen hormone, through its neuroprotective action

in women, is responsible for some of the reported differences and similarities in both global functioning and quality of life. Thus far, the data has not determined a causal role for estrogen hormone, because there could be other factors involved, for example male/female personality traits and gender roles. As has been shown, some studies have demonstrated that the addition of estradiol to anti-psychotics in the treatment of schizophrenia in females increased the efficacy of the treatment, which suggests that estrogen hormone may have a role in future therapy, and does indeed have aneuroprotective action, however the use of ex oogenus estrogen hormone has been restricted to date because of concern regarding side effects. Exogenous estrogen hormone therapy carries risks of thromboembolism, endometrial cancer, breast cancer and stroke. Nor have any trials been reported of estrogen hormone for use in 'at ultra-high-risk mental states', perhaps because of concern regarding side effects.

Conclusions

The researchers concluded that the addition of 100 micrograms of estrogen hormone, delivered via a patch to standard treatment, significantly reduced positive and general psychotic symptoms during the four-week trial compared to standard treatment alone.

The potential therapeutic utility of selective estrogen hormone receptor modulators in schizophrenia is increasingly being recognized. Estradiol, which is selectively agonistic to estrogen receptors in the brain and bones was useful to improve not only negative, positive, and general psychopathological symptoms, but also cognitive functions, without having the side effects of neuroleptics. Nevertheless, treatment with selective estrogen hormone receptor modulators is associated with small risk of endometrial cancer and venous thromboembolism. The article indicates Estradiol as a potential adjunctive treatment strategy for chronic schizophrenia both in female and male patients, however potential negative long-term implications of treatment should be considered.

Decisions about whether estrogen therapy should be used routinely in the management of schizophrenia need to be guided by further research, in particular, it will be necessary to carefully evaluate the risk-benefit ratio and cost-effectiveness of this treatment. However, the study of the 'Estrogen Hypothesis 'has given us a deeper insight into the mechanisms of the development of psychotic illness.

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